Heterocyclic Letters
Vol. 7| No.1|177-181|Nov-Jan| 2017
ISSN : (print) 2231–3087 / (online) 2230-9632
CODEN: HLEEAI
http://heteroletters.org

EFFICIENT SYNTHETIC METHODS OF THIOBENZIMIDAZOLE SUBSTITUTED QUINAZOLIN-4(3H)-ONE

Md. Rafeeq[1], Ch.Venkata Ramana Reddy[1*] and M. Vinodini[2]

[1]Department of Chemistry, Jawaharlal Nehru Technological University Hyderabad, Kukatpally, Hyderabad, – 500085, Telangana, India
[2]Department of Chemistry, RBVRRW College, Narayanaguda, Hyderabad-500029.
*Email: vrr9@yahoo.com (*corresponding author)*

ABSTRACT

Condensation of 2-((1H-benzo[d]imidazol-2-yl)thio)acetic acid (**1**) with *o*-aminobenzamide (**2**) gave 2-[1-(1H-benzimidazol-2-yl)-ethylsulfanyl]-3*H*-quinazolin-4-one (**3**). The latter could also be prepared by the reaction of 2-(chloromethyl)quinazolin-4(3H)-one (**4**) with 1H-benzo[d]imidazole-2-thiol **(5)** either in acetone containing triethylamine or in DMF containing K_2CO_3 in the presence of TBAB as phase transfer catalyst. **3** could also be prepared by an alternative method involving the reaction of **4** with potassium ethylthioxanthate yielding O-ethyl S-((4-oxo-3,4-dihydroquinazolin-2-yl)methyl)carbonodithioate (**6**) and subsequent condensation of the latter with *o*-phenylenediamine **(7)** in the presence of trifluroacetic acid (TFA), under reflux in toluene. **5** required in this work was obtained from the commercially available 7 under refluxing conditions with potassium ethylxanthate in ethanol for 2 hr. **1** was prepared by reaction of 5 with 2-chloroacetic acid in aq. NaOH at RT whereas **4** was obtained from **2** and chloroacetyl chloride followed by refluxation in acetic acid for 3 hr. The structures of all the new compounds synthesized in the work have been established on the basis of their spectroscopic data.

KEYWORDS

Anthranilamide, 2-Thioquinazolinone, 2-Chloromethyl-3*H*-quinazolin-4-one, Chloroacetic acid, Triethylamine.

INTRODUCTION

The quinazolinone ring system forms an important class of N-heterocyclic compounds as it is present in a large number of compounds with useful biological properties such as anti-inflammatory[I-II], anticonvulsant[III], hypotensive[IV] and anti-malarial[V] types. 2-Thioquinazolinones possess good analgesic activities[VI]. 2-Heterylquinazolin-4(3*H*)-ones exhibit a wide range of pharmacological properties[VII-VIII] such as good antimicrobial activity against different species of gram-positive bacteria[IX], gram-negative bacteria[X], pathogenic

fungi[XI-XII]. In view of this wide range of pharmacological activities, the quinazolinone derivatives have been the target of a large number of organic synthetic efforts[XIII-XVI].

In view of these observations and work on quinazolinones it was considered worthwhile to study the reaction of **1** with heterocyclic compound such as 2-mercaptobenzimadazole and subsequent chemical modifications of the condensation products as new chemical entities with potential biological activities.

RESULTS AND DISCUSSION

Condensation of 2-((1H-benzo[d]imidazol-2-yl)thio)acetic acid (**1**) with commercially available anthranilamide (**2**) under refluxing conditions in aq. HCl for 12 hr gave a product which has been characterized as 2-(1H-benzoimidazol-2-ylsulfanylmethyl)-3H-quinazolin-4-one (**3**). The structure of **3** was established on the basis of its spectral and analytical data. Thus, its IR (KBr) showed a very broad band in the region 3200 cm^{-1} due to –NH- stretching vibration and a very strong, sharp peak at 1650 cm^{-1} due to the amide carbonyl group. Its ^1H NMR (DMSO-d_6) spectrum showed signals at δ 4.53 (s, 2H, -CH_2-), 7.14-8.11 (m, 8H, aryl protons) and at 12.65 (broad, s, 2H, D_2O exchangeable protons 2×–NH-). Its ^{13}C-NMR spectrum (DMSO-d_6/TMS) showed signals at δ 34.83, 114.05, 121.11, 121.67, 125.85, 126.63, 126.89, 134.44, 139.49, 148.40, 149.75, 153.95 and 161.67. Its LCMS spectrum showed the molecular ion peak at 309 corresponding to a molecular mass of 308 when recorded in the Q+1 mode.

Condensation of 1H-benzimidazole-2-thiol (**5**) with 2-chloroacetic acid in aq. NaOH at RT gave (1H-benzoimidazol-2-ylsulfanyl) acetic acid (**1**). The structure of **1** was established on the basis of its spectral and analytical data. Thus, its IR (KBr) showed a very broad band in the region 3200-3100 cm^{-1} due to –NH- stretching vibration and a strong, sharp peak at 1670 cm^{-1} due to the carbonyl group as a diagnostic absorption. Its ^1H NMR (DMSO-d_6) showed signals at δ 5.4 (S, 2H, -CH_2-), 7.2-8.00 (m, 4H, aryl protons) and at δ 12.85 (broad, s, 1H, D_2O exchangeable protons –NH-) 12.85 (broad, s, 1H, D_2O exchangeable protons -COOH). Its LCMS spectrum showed the molecular ion peak at 209 corresponding to a molecular mass of 208 when recorded in the Q+1 mode.

In an alternative approach, reaction of **5** with **4** under different conditions in the presence of bases at RT for 2-4 hr gave **3**, which is identical in m.p. TLC and IR with that of the same product obtained in the route described above, ie.**1**+**2** ⟶ **3**. **4** itself was obtained by reaction of **2** with 2-chloroacetic acid in aq.NaOH at RT for 3 hr. **4** is known in literature but it has been characterized in our work by spectral methods.

In an yet alternative approach, **3** could be prepared by the condensation of dithiocarbonic acid o-ethyl ester S-[2-(4-oxo-3, 4-dihydroquinazolin-2-yl) ethyl] ester (**6**) with **7** in refluxing toluene containing traces of trifluoroacetic acid (TFA) as catalyst. The former compound. i.e. **6**, in turn, were synthesized by the reaction of **4** with potassium *o*-ethyl dithiocarbonate in ethanol at RT for 3 hr in 65% yield. (**Scheme–I**).

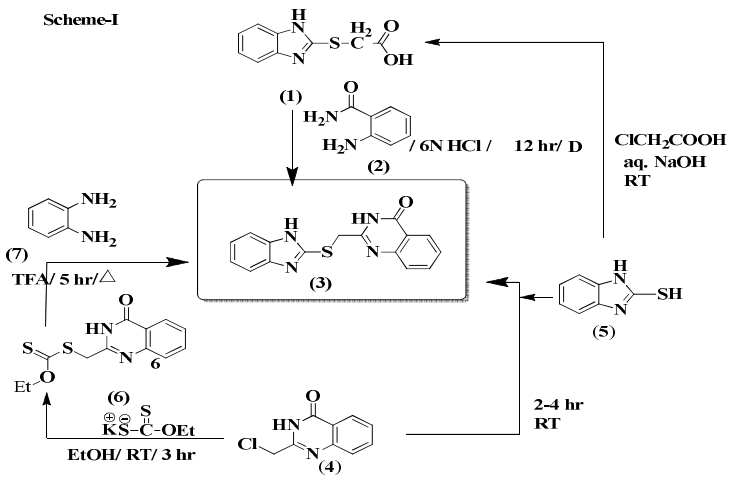
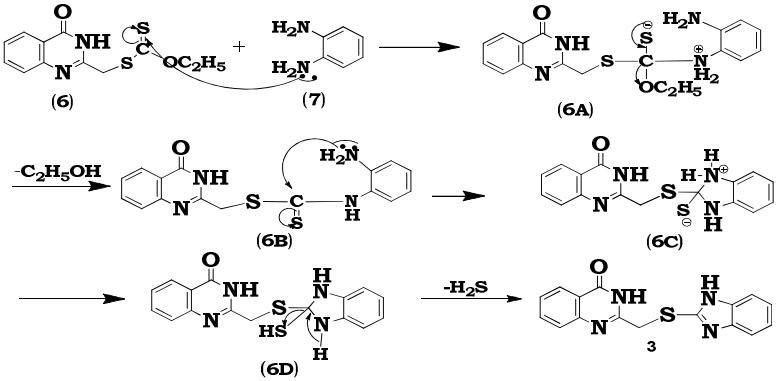


Table: 1 Preparation of **3** from **5** and **4** in different Condition

S.No.	Solvent used	Base used	Time (hr)	Yield of **3**(%)
1.	Water	(5%) K_2CO_3 (5 mole %)	4	55
2.	Water	(5%) NaOH (5 mole %)	4	60
3.	Water	(5%) KOH (5 mole %)	4	60
4.	PEG-600	-	3	70
5.	MeOH	NaOH (5 mole %)	3	90
6.	Acetonitrile	TEA	3	75
7.	DMF	K_2CO_3 (5 mole %)	2	75
8.	MeOH	Piperidine	3	75
9.	MeOH	Pyridine	3	60
10.	DCM	TEA	3	70
11.	$CHCl_3$	TEA	3	70

It is obvious from the **Table-1** given above, that for the condensation of **5** with **4**, 5% methanolic NaOH seems to offer the best conditions giving 3 in highest yield. All the reactions described in this paper are neatly depicted in Scheme-I

The conversion of **6** to **3** seems to follow the mechanism given in **Scheme-II**



….Scheme–II

The mechanism probably involves the nucleophilic attack by the amino group of **7** on the xanthate carbon of **6** yielding the intermediate **6A** that loses elements of ethanol to form **6B**. The latter, then, undergoes ring closure involving a second but intramoleular, nucleophilic attack by the amide amino group on the xanthate carbon to form **6C** which changes to **6D**. This intermediate then undergoes loss of elements of H_2S, in a bid to aromatize, to form the final product **3**.

EXPERIMENTAL SECTION

General Conditions. Melting points are uncorrected and were determined in open capillary tubes in sulphuric acid bath. TLC was performed on silica gel-G and spotting was done using iodine or UV-light. IR spectra were recorded with Perkin-Elmer 1000 instrument in KBr phase, ^{1}H-NMR on VARIAN 400MHz instrument and Mass spectra on Agilent-LC-MS instrument giving only $M^{+\cdot}$ Values using Q+1or Q-1 mode.

Preparation of 3 from 1 and 2: A mixture of 1 (5 mM) 2 (5 mM), and aq. HCl 50 ml (6N) was refluxed for 12 hr. At the end of this period, the reaction mixture was diluted with water (2×25 mL) and pH adjusted to ≥ 7.0 with aq. ammonia (1:1, 5 mL). The separated solid was filtered, washed with water (2×20 mL) and dried to obtain **3**. Yield = 3.10 gms (72%); M.P. 164-168 °C(MeOH) (For experimental data please under Results and Discussion).

Preparation of 3 from 5 and 4 using different bases:

A mixture of **5** (10 mM), **4** (10 mM), base (5 mM) and solvent (25mL) was stirred at RT for 2-4 hr. After completion of the reaction, as monitored by TLC, the mixture was poured into ice-cold water. The separated product was filtered, washed with water, dried. For yields see under the **Table: 1**

Preparation of 3 from 6 and 7 (Alternate method)

A mixture of **7** (5 mM), **6** (5 mM), TFA (1 mM) and toluene (30 mL) was refluxed at 110 °C in an oil-bath for 5 hr until the reaction was complete as shown by TLC. At the end of this period, toluene was distilled off, and the residue treated with aq. NaOH solution (1N 50 mL) at RT. The separated solid was filtered, washed with water and dried.

Preparation of (4-oxo-3, 4-dihydroquinazolin-2-ylmethyl)dithiocarbonic acid ethyl ester (6) from 4:

A mixture of **4** (1.94 g, mM), potassium ethoxydithiocarbamate (1.60 g, mM) and ethanol (30 mL) was refluxed for 3-4 hr. Then, the reaction mixture was cooled to RT and the separated KBr salt was filtered and washed with ethanol (20 mL). The ethanolic filtrate was distilled off and the residue diluted with water (20 mL). The separated solid was filtered, washed with water (20 mL) and dried to obtain crude **6**. The latter was recrystallised from hot isopropanol to obtain pure 6.

6: Yellow solid; Yield = 1.68 g (60%); mp. = 157-59 °C; IR (KBr): 3200-3100 cm^{-1} (very broad, –NH-), 1660 cm^{-1} (strong, sharp, C=O of the amide group), 1180 cm^{-1} (broad, C=S of the xanthate group). ^{1}H-NMR (DMSO-d_6/TMS): δ 1.20 (t, J=7.02 Hz, 3H, -CH_2-C**H$_3$**), 4.40 (s, J=7.02 Hz, 2H, -C**H$_2$**-CH_3), 4.50 (s, 2H, -C**H$_2$**-), 7.20-8.50 (complex, m, 4H, **aryl protons**) 12.58 (broad s, 1H, D_2O exchangeable proton, –N**H**). LCMS: m/z = 281 ($M^{+\cdot}$ +1).

CONCLUSION

In conclusion, synthesis of novel 2-(1H-benzoimidazol-2-ylsulfanylmethyl)-3H-quinazolin-4-one (**3),** three different routes have been achieved. Of all the methodologies discussed, the condensation of **5** with **4** MeOH containing NaOH as base appears to be the better & efficient route for the product obtained, compared to the other routes.

ACKNOWLEDGEMENT

The authors are indebted to the University Grants Commission, Govt. of India, New Delhi for financial support. They are also thankful to the authorities of Jawaharlal Nehru Technological University Hyderabad for providing laboratory facilities.

REFERENCES

I. Alagarasamy, M.; Meena, S.; Revathi, R.; KumarS.V.; and Ramesh, K. V. *Arkivoc.* **2006**, *58*, 149.

II. Ozaki, K.; Yamada, Y.; Oninell, T.; Ishizuka, T.; Iwasawa, Y. *J. Med .Chem.* **1985**, *28,* 568.

III. G. Bonola, P. Dare, M. J. Mgistretti, E. Massarani and I. Setnikar, *J. Med. Chem.,* 11, **1968**, 1136.

IV. Hess, H. J.; Cronin, T. H.; Scriabine, A. *J. Med. Chem.* **1968**, *11*, 130.

V. Bhargava, P. N.; Chaurasia, M.R. *J. Med. Chem.* **1968**, *11*, 404.

VI. Reddy, P. S. N.; Venugopal, K. N.; Rao, G. K. and Pai, P. N. S. *Indian. J. Heterocycl. Chem.* **2007**, 12, 243.

VII. Badaway, E. L.; Syed, A. M.; Rida, S. M.; Sliman, F. S. G.; and Thomas, T. *Monat. Chem.* **1989**, 120, 1159.

VIII. Murgan, V.; Thomas, C.; Ramasarma, G. V. S.; Kumar, E. P. *Indian J. Pharm. Sci.* **2003**, *65*, 386.

IX. Y. Zhou, D. E. Murthy, Z. Sun and V. E. Gregor, *Tetrahedron. Lett.,* 45, **2004**, 8049.

X. A. M. A. Fatmah, A. A. Lalila, N. N. Mahmoud, E. H. El-Sayed, A. A. M. Abdel-Aziz, A. S. El-Azab, S. G. Abdel-Hamide, M. A. Al-Omar, A. M. Al-Obaid, and H. I. El-Subbagh, *Bioorg. Med. Chem. Lett.* 18, **2010**, 2849.

XI. S. N. Pandeya, D. Sriram,; G. Nath, and E. De Clerck, *Pharm. Acta. Helv.* 74, **1999**, 11.

XII. G. Grover and S.G. Kini, *Eur. J. Med. Chem.,* 41, **2006**, 256.

XIII. P. M. Chandrika, T. Yakaiah, A. R. Rao, B. Narasiah, N.C. Reddy, V. Sridhar, J.V. Rao, *Eur. J. Med. Chem.* 43, 2008, 846.

XIV. S. L. Cao, Y.P. Feng, Y. V. Jiang, G.Y. Liu Ding and R.T. Li, *Bioorg. Med. Chem. Lett.,* 15, **2005**, 1915.

XV. J. Li, Y. Meng, Y. Liu and Z. Feng, *Invest. New Drugs.* **2010**, 28, 132-138.

XVI. K. M. Foote, A. A. Mortlock, N.M. Heron, F. H. Jung,G. B. Hill, G. Pasquet, M.C. Brady, S. Green,S.P. Heaton, S. Kearney, N.J. Keen, R. Odedra, S.R. Wedge and R.W. Wikinson, *Bioorg. Med. Chem. Lett.,* 18, **2008**, 1901.

Received on November 9, 2016.